Ultra-protective ventilation combined with V-V ECMO has a preferable therapeutic effect on Acute Respiratory Distress Syndrome: An experimental study in aged Beagle dogs

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Abstract

Background To assess the optimal mechanical ventilation strategies during venovenous extracorporeal membrane oxygenation (V-V ECMO) in aged dogs with severe respiratory distress syndrome.

Methods Beagle dogs aged 10-12 years old were randomized assigned(n = 6 per group) to control or three different ventilation strategy groups: conventional ventilation strategy (CV) group, protective ventilation strategy (PV) group and ultra-protective ventilation strategy (UPV) group. ARDS model was established and V-V ECMO was used in all the dogs of CV, PV and UPV groups. Gas exchange data including blood partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and ventilator-induced lung injury(VILI) data including airway plateau pressure (Pplat), extravascular lung water index (EVLWI) and lung compliance were continuously monitored. After continuous treatment for 24 hours, lung tissue were collected to assess the histological examination and the inflammatory factors expression.

Results For VILI data, the 24-hour lung compliance of UPV group was significantly higher than CV and PV groups. Pplat and EVLWI were significantly lower in UPV group than those in the other two ventilation strategy groups. And the pathology study demonstrated that lower lung injury scores of the UPV group than the CV or the PV group. Results of immunohistochemistry showed that the expression of IL-6, IL-10, and TNF-α were significantly lower in UPV group than PV and CV groups, which further confirmed the effectiveness of UPV strategy.

Conclusions UPV strategy showed significant advantage on decreasing lung injury and the inflammatory responses in the aged dog of severe ARDS model supported with V-V ECMO.

Background

Acute respiratory distress syndrome (ARDS) is a fatal complication which represents as progressive and resistant hypoxia or hypercapnia clinically and as impairment of pulmonary capillary and alveolar endothelial cells pathologically[1]. ARDS is generally caused by trauma, infection, acute severe pancreatitis and critical post-operative complications of cardiothoracic surgeries[2–4]. Especially in the past 3 years, the coronavirus disease 2019 (COVID-19) pandemic has infected more than 400 million individuals till March 2022, and killed more than 6.1 million individuals globally caused by ARDS or multiple organ failure. It has been shown that the incidence rates and the deadly cases of ARDS increase dramatically with age[5–8], however, age-dependent treatment strategies in ARDS are lacking.

Mechanical ventilation(MV) plays a critical role in the management of ARDS. However, studies from the past few decades showed that, the ventilator-induced lung injury(VILI) resulting from shear stress and high airway plateau pressure (Pplat) may induce pulmonary and systemic inflammatory response through a complex interplay between tissue deformation, mechanotransduction and edema[9]. Data suggested a higher incidence of VILI in elderly population because of the changes within the respiratory system[7, 10]. Lower tidal volume ventilation strategy has been shown to be associated with decreased VILI incidents, however, this is poorly adhered to among clinicians. Veno-veno extracorporeal membrane

oxygenation (V-V ECMO) has become a widespread therapy for ARDS in COVID-19.The use of V-V ECMO may minimize VILI through reducing the need for MV in gas exchange[11].

The combination MV with V-V ECMO strategy in treating Covid-19 and ARDS was recommended in some consensus guidelines. However, given varied selection criteria, outcomes, and baseline characteristics, the optimum ventilatory settings in ARDS during ECMO are controversial[12, 13]. Few data about the ventilatory strategies of ARDS with V-V ECMO in elderly population. We performed a aged animal model to estimate the different ventilatory strategies effects on the ARDS clinical outcomes.

Methods

Chemicals and reagents

Oleic acid was obtained from Sigma-Aldrich (PHR1586). The anti-IL-6 antibody (ab 193853) was purchased from Abcam, aiti-IL-10 antibody(148801) and TNF-α antibody(E10041) were purchased from ThermoFisher.

Animals model and experimental protocol

Ethics The study was approved by the Committee of Animal Care and Use of Naval Military Medical University, and all procedures were performed according to the National Institutes of Health Guidelines.

Anesthesia and surgical preparation A total of 24 healthy male beagles aged at 10–12 months, weight around 10–15 kg were obtained from the Laboratory Animal Center of Naval Military Medical University (Shanghai, China). All the dogs were fasted at least 8 hours before anesthetic. Anesthesia induction was performed with an intravenous injection of 30 mg/kg sodium pentobarbital and maintained with propofol during the study period. After intubation with a cuffed endotracheal tube (8.0 mm inner diameter), the dogs were connected mechanical ventilators (Bird® 6400 ventilator, Sti model, USA). The initial MV settings were as follows: FiO_2 60%, VT (Tidal volume) 10 mL/kg, PEEP (Positiveend-expiratory pressure) 5 cmH_2O, RR (Respiratory rate) 20 bpm, I: E 1:2. The right internal jugular vein, right femoral artery and right femoral vein were surgically exposed for insertion of Swan-Ganz catheter, PiCCO (Pulse indicator continuous cardiac output) Pulsiocath catheter (PC8500, Shanghai) and femoral artery catheter respectively. After completing all preparation above, baseline data was collected.

Induction of lung injury and V-V ECMO support After anesthesia and intubation, 99% oleic acid (0.2 mL/kg) was pumped into jugular vein and injected repeatedly if necessary until PaO_2/FiO_2 in arterial blood felt below 100 mmHg. A stable severe ARDS model was established when the PaO_2/FiO_2 remained less than 100 mmHg for 30 min. Dogs were heparinized and cannulated on right jugular and femoral vein to build up V-V ECMO. The circulation started when ARDS models were created. Parameters of ECMO were set as: pump flow rate 70 mL/kg, gas flow rate 2 L/min, FiO_2 60%, activated clotting time (ACT): 180 ~ 220 s.

Study groups

All the individuals were divided into different groups according to its mechanical ventilation strategy as follow:

Control group (Control): n = 6, CTL animals received neither lung injury nor ECMO. Ventilation parameter set as FiO_2 60%, VT 10 mL/kg, PEEP 5 cmH2O, Respiratory rate(RR) 20 bpm, I:E 1:2.

Conventional ventilation group (CV): n = 6, ventilation parameter set as FiO_2 60%, VT 10 mL/kg, PEEP 5 cmH_2O, RR 20 bpm, I:E 1:2.

Protective ventilation group (PV): n = 6, ventilation parameter set as FiO_2 60%, VT 6 mL/kg, PEEP 10 cmH_2O, RR 20 bpm, I:E 1:2.

Ultra-protective ventilation group (UPV): n = 6, ventilation parameter set as FiO_2 40%, VT 3 mL/kg, PEEP 10 cmH_2O, RR 8 bpm, I:E 1:2.

Measurements

All measurements of respiratory mechanics and hemodynamic variables were collected at the baseline, and at 0 minute, 5 minutes, 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 12 hours, 18 hours and 24 hours after ARDS models established. Dogs were executed by potassium chloride bolus (mercy killing) and lung tissue were collected at 24 hours of the study period. Samples were obtained separately from the upper lobe, middle lobe and ventral, lateral and dorsal sections of the right lower lobe. Tissue sections with 5 μm thick were prepared and stained with hematoxylin and eosin(HE) for pathological analysis after fixed with 4% paraformaldehyde. The HE slices were examined by two pathologists blinded to the group allocations. To assess lung injury, a validated score was used to evaluate by the following[14]: alveolar disruption, neutrophil infiltration, edema and hemorrhage; each of these categories received a score ranging from 0 to 3, where 0 corresponds to no pathologic alteration, 1 corresponds to mild, 2 corresponds to moderate and 3 corresponds to severe pathologic alteration. Twenty random areas were evaluated for each section at 200x magnification and its values averaged.

Immunohistochemistry assay of lung tissue was used to determine the expression of IL-6, IL-10 and TNF-α. Samples embedded with paraffin were cut into 5 μm thick sections and were blocked with 3% normal non-immune serum after deparaffinized and dipped in the sodium citrate. Then the sections were incubated with primary antibodies (1:100) at 4°C overnight following by an incubation with HRP-conjugated secondary antibodies for 30 min at 37°C. Lastly, the sections were incubated with DAB substrate and counterstained with hematoxylin. The protein expression were analyzed using integrated optical density (IOD) with Image Pro Plus 6.0 software.

Statistical analysis

Data expressed as mean ± standard and were analyzed statistically by using SPSS 24.0 software, to be considered with statistical difference exists when $P < 0.05$ (95% CI, dual). Data error of the mean longitudinal data was analyzed using repeated measures two-way ANOVA, followed by Tukey's multiple comparisons test. Single time point data were compared using one-way ANOVA or *t* tests. Comparison of the continuous date within the same group were evaluated by Paired *t* tests.

Results

A total of 24 beagles aged 10–12 years old were used and randomized assigned into control, CV, PV, and UPV groups (Fig. 1). The character of Beagle's of age and weight were shown in supplementary material Table S1. There were no significant differences in four groups at baseline in weight, PaO_2/FiO_2, PCO_2 and lung compliance at baseline (Table 1).

Table 1
Baseline of individuals at baseline.

Parameter\Group	CTL (n = 6)	CV (n = 6)	PV (n = 6)	UPV (n = 6)
Weight (kg)	12.6 ± 1.64	13.07 ± 1.19	12.83 ± 0.97	12.57 ± 1.59
Age (years)	11.47 ± 0.53	11.33 ± 0.63	11.58 ± 0.48	11.22 ± 0.49
PO_2/FiO_2 (mmHg)	417.2 ± 68.7	437.2 ± 37.1	394.2 ± 47.9	415.3 ± 59.6
PCO_2 (mmHg)	40.1 ± 2.3	37.7 ± 2.9	39.6 ± 3.0	38.6 ± 2.0
Lung compliance (mL/cm H_2O)	30.3 ± 2.3	31.1 ± 2.7	31.1 ± 1.3	30.3 ± 2.9
Pplat (cmH_2O)	13.1 ± 0.5	12.9 ± 1.0	12.0 ± 0.9	12.6 ± 0.7
MAP (mmHg)	111.3 ± 10.3	105.9 ± 11.0	102.7 ± 10.0	109.5 ± 6.3
CVP (mmHg)	13.1 ± 2.5	14.1 ± 3.2	13.9 ± 2.5	13.0 ± 2.0
EVLWI (mL/Kg)	6.7 ± 1.4	7.2 ± 1.8	6.5 ± 1.6	7.0 ± 1.1
Heart rate (beats/min)	149.9 ± 14.5	141.3 ± 18.8	149.6 ± 18.3	139.0 ± 17.6

Abbreviations: CV = conventional ventilation strategy group, PV = protective ventilation strategy group, UPV = ultra-protective ventilation strategy group, PaO_2/FiO_2 = partial pressure of arterial O_2 to fraction of inspired O_2 ratio, $PaCO_2$ = partial pressure of arterial CO_2, MAP = mean artery pressure, CVP = central venous pressure, EVLWI = extravascular lung water index.

Effects of different MV strategies on respiratory and hemodynamic variables

Lung injury induction led to severe hypoxia, the PaO_2/FiO_2 decreased below 100 mmHg after ARDS induction without any differences between three injured groups at T_0 (Table 2). After connected to V-V

ECMO for 5 minutes, PaO_2/FiO_2 increased rapidly in three injured groups to 150 mmHg, and continued to maintain over 300 mmHg throughout the study period since T_{2h}, which indicating that the improvement of oxygenation was effective by using V-V ECMO. PaO_2/FiO_2 in three ARDS model groups were lower than in control group, but there are no difference between three injured groups until 24h (Fig. 2A and supplementary material Table S2). In contrast, lung compliance decreased significantly after ARDS induction while remained low during study period in CV group and increased slightly after connected to V-V ECMO in PV and UPV groups (Fig. 2B and Table 4). It showed that the lung compliance in UPV group was significant higher compare to CV and PV groups. Pplat increased in response to lung injury, and continued to increase throughout the study period in CV group. But in UPV and PV groups, it decreased gradually after connected to V-V ECMO. Pplat was lower in UPV group than that in PV and CV groups since T_{1h} till T_{24h}(Fig. 2C and Table 4). The other ventilation kinetic parameters of PCO_2 were similar in different groups during all the experiment period (Fig. 2E and supplementary material Table S3). The hemodynamic parameters of mean artery pressure(MAP) and central venous pressure (CVP) haven't change after lung injury and were similar in four different groups (Table 5). But the EVLWI significantly increased after lung injury, and maintained at very high level in PV and CV groups while decreased gradually in UPV group(Fig. 2D and supplementary material Table S4).

Table 2
Respiratory parameters at T_0.

Parameter\Group	CTL (n = 6)	CV (n = 6)	PV (n = 6)	UPV (n = 6)
PO_2/FiO_2 (mmHg)	425.8 ± 41.6	72.5 ± 10.1*	52.2 ± 21.2*	67.9 ± 13.8*
PCO_2 (mmHg)	42.6 ± 3.0	39.1 ± 2.1	40.3 ± 1.9	42.9 ± 2.2
Lung compliance (mL/cmH_2O)	31.0 ± 2.5	15.7 ± 1.8*	12.3 ± 1.2*	16.3 ± 2.1*
Pplat (cmH_2O)	12.3 ± 0.7	31.7 ± 1.1*	32.7 ± 1.3*	31.3 ± 2.0*

Abbreviations: CV = conventional ventilation strategy group, PV = protective ventilation strategy group, UPV = ultra-protective ventilation strategy group, PaO_2/FiO_2 = partial pressure of arterial O_2 to fraction of inspired O_2 ratio, $PaCO_2$ = partial pressure of arterial CO_2, Pplat = plateau pressure. * $p < 0.05$ compared to Control.

Table 3
Hemodynamic parameters at T_0.

Parameter\Group	CTL (n = 12)	CV (n = 12)	PV (n = 12)	UPV (n = 12)
MAP (mmHg)	109.3 ± 8.2	103.8 ± 7.4	108.0 ± 6.0	102.7 ± 5.1
CVP (mmHg)	12.3 ± 1.6	8.7 ± 2.2	10.1 ± 2.9	7.3 ± 2.0
EVLWI (mL/Kg)	6.8 ± 1.2	23.5 ± 3.1*	22.7 ± 4.1*	24.5 ± 3.0*
Heart rate (beats/min)	152.9 ± 15.9	161.0 ± 19.3	159.7 ± 18.3	155.3 ± 20.1

Abbreviations: CV = conventional ventilation strategy group, PV = protective ventilation strategy group, UPV = ultra-protective ventilation strategy group, MAP = mean artery pressure, CVP = central venous pressure, EVLWI = extravascular lung water index. * $p < 0.05$ compared to Control.

Table 4
Respiratory parameters at T_{24h}.

Parameter\Group	CTL (n = 6)	CV (n = 6)	PV (n = 6)	UPV (n = 6)
PO_2/FiO_2 (mmHg)	433.8 ± 41.1	334.7 ± 88.5*	315.6 ± 65.0*	370.8 ± 46.5*#
PCO_2 (mmHg)	40.5 ± 2.0	37.9 ± 3.1	41.2 ± 2.9	42.0 ± 2.2
Lung compliance (mL/cmH_2O)	30.7 ± 2.0	12.6 ± 1.9*	15.7 ± 1.7*	21.8 ± 1.1*#
Pplat (cmH_2O)	11.9 ± 1.1	35.6 ± 2.0*§¥	27.9 ± 1.5*§¥	18.3 ± 0.9*#

Abbreviations: CV = conventional ventilation strategy group, PV = protective ventilation strategy group, UPV = ultra-protective ventilation strategy group, PaO_2/FiO_2 = partial pressure of arterial O_2 to fraction of inspired O_2 ratio, $PaCO_2$ = partial pressure of arterial CO_2, Pplat = plateau pressure. * $p < 0.05$ compared to Control, # $p < 0.05$ compared to PV group.

Table 5
Hemodynamic parameters at T_{24h}.

Parameter\Group	CTL (n = 12)	CV (n = 12)	PV (n = 12)	UPV (n = 12)
MAP (mmHg)	105.0 ± 10.2	101.9 ± 8.2	102.3 ± 9.9	104.7 ± 8.1
CVP (mmHg)	12.0 ± 1.1	10.7 ± 1.2	10.3 ± 2.4	8.8 ± 1.0
EVLWI (mL/Kg)	6.7 ± 1.0	19.3 ± 3.8*	16.5 ± 4.2*	9.2 ± 2.4*#
Heart rate (beats/min)	132.5 ± 13.6	141.6 ± 18.0	139.4 ± 15.0	129.7 ± 18.8

Abbreviations: CV = conventional ventilation strategy group, PV = protective ventilation strategy group, UPV = ultra-protective ventilation strategy group, MAP = mean artery pressure, CVP = central venous pressure, EVLWI = extravascular lung water index. * $p < 0.05$ compared to Control, #$p < 0.05$ compared to PV group.

UPV strategy ameliorated lung injury of ARDS

It showed that hemorrhage, edema and consolidation widely spread over the whole lungs in three injured groups. The representative ARDS lung specimen showed more severe injuries of hemorrhage, edema and consolidation. The UPV group showed less hemorrhage, edema and consolidation than PV and CV groups (Fig. 3A).

Pathological samples were made with HE stain, which are shown in Fig. 3. CV group showed widely and obviously rupture of capillaries and hemorrhage, edema, disruption and collapse of alveolar, while hemosiderin spotted deposited massively in interstitial under high power lens. PV group showed milder pathological changes as alveolar partly complete, less edema and hemosiderin deposition than CV. UPV group showed minimally pathological changes, alveolar were partly collapsed while hemosiderin deposited and edema were mildest among three groups (Fig. 3B, C). All the three injured groups had significantly higher scores compared to the control group. In terms of the injured groups, the scores of lung injury was lower in the UPV group than CV and PV groups (Fig. 3D).

UPV strategy attenuates inflammatory response of ARDS

Immunohistochemistry assay was used to determine the expression of IL-6, IL-10 and TNF-α in lung tissue, which were shown in Fig. 4A-F. The expression of IL-6, IL-10 and TNF-α were increased in three injured groups compared to control group. But the expression of IL-6, IL-10, and TNF-α were significantly lower in UPV group than the other two groups (Fig. 4G). It is obviously that the results of immunohistochemistry further confirmed the protective effect of UPV strategy.

Discussion

Within the past several decades, epidemiological studies have reported that the incidence of ARDS is higher in the elderly population and is associated with higher mortality. Even the outcomes of patients with ARDS have been improved over time, but the mortality rate for ARDS in elderly population still remains a high mortality rate. Mechanical ventilation plays critical role in the management for ARDS, however, elderly population showed increased susceptibility to multiple organ dysfunction, systemic inflammation and death induced by VILI[7, 10, 15]. For reducing the VILI, ECMO was applied to ensure adequate gas exchange for severe ARDS patients[16]. But the effects of ventilation combined with ECMO therapy are unclear. The clinical studies of ARDS rarely include substantial numbers of elderly patients. Given the difficulties in randomized clinical studies, aged Beagle dogs of severe ARDS model were used in our study to explore the optimal MV settings in elderly population of ARDS.

We designed an experimental study to compare the ultra protective ventilation strategy versus protective ventilation strategies in its ability to modulate lung injury and inflammatory response. The conventional ventilation strategy and none -ARDS animals group were used as positive and negative control to confirm the results. We demonstrated that even protective ventilation strategy still induced severe lung injury and inflammatory response, which can be ameliorated by applying ultra protective ventilation.

It is reported that near-apneic ventilation can decrease lung injury in an adult pig ARDS model with ECMO[17]. But near-apneic ventilation strategies require higher FiO_2 to improve oxygenation, and patients should be sedated without spontaneous breathing, which can lead to atelectasis and inflammation[13]. Thus, in our study, we designed a ultra protective ventilation instead of near-apneic ventilation strategy to reduce VILI of ARDS.

Pplat, ELWI, lung compliance and lung injury scores were collected in this study to evaluate the efficacy of MV strategies in ARDS model undergoing V-V ECMO. High Pplat is an independent risk factor of mortality in ARDS patients, especially those with a Pplat over 30 cmH_2O means a poor prognosis[18]. Clinical studies and animals experiments showed that ARDS mortality reduces when Pplat is decreased and this relationship appears to be linear. Current recommendation by the ARDS net for ARDS suggested a protective ventilation strategy based on limitation of Pplat to 30 cmH_2O. However, recent studies have shown that, even Pplat was lower than 30 cmH_2O, patients with ARDS may still be at risk of VILI and hyperinflation station[19]. Our study showed that conventional ventilation strategy leads to a Pplat around 35 cmH_2O, and even in protective ventilation strategy group, the Pplat was still very high over 25 cmH_2O. We demonstrated that Pplat- only around 18 cmH_2O in ultra protective ventilation group, which was significantly lower than in protective ventilation strategy group. ELWI is a parameter representing edema of lung which indicates the severity of ARDS. In this study, ELWI of the three injured groups reached climax early after 5 minutes ECMO circulation, and then reduced gradually. We demonstrated that an obvious decreasing were found in UPV groups than the other two injured groups after 12 hours of connecting to MV. In our study, lung compliance declined about 50% in response to ARDS induction in three injured groups. Even after connected to V-V ECMO and MV, lung compliance was further reduced in CV group, which indicating that the conventional ventilation strategy may cause secondary damage to lung. We discovered that lung compliance of UPV group was increased and maintained steady in the study period, which was the same as pathological results of mildest changes. It showed that in UPV group, the injury scores were significantly lower than in the other two injured groups.

In spite of different etiologies, inflammatory response is the common mechanism of ARDS, which leads to high permeability of pulmonary capillaries, alveolar/interstitial edema and effusion, inflammatory cells infiltration and hyaline membrane formation[20–22]. Plenty of studies demonstrated the relation between elevated cytokines concentrations and mortality in ARDS[23]. It has proven that cytokine storm induces in ARDS elderly patients was more common than in young patients[24]. The inflammatory cytokines including IL-6, IL-8 and TNF-α were analyzed in our study. We showed that UPV strategy, with lower VT, FiO_2 and RR, demonstrated a significant decrease in IL-6, IL-8 and TNF-α production, which indicating that ultra-protective ventilation strategy can give full lung protection against the damage induced by mechanical ventilation and ARDS.

There are still some limitations of this study. First, the sample capacity was small, we have got only 6 individuals in different ventilation strategy groups. Second, the treatment lasted for only 24 hours due to the difficulty on transfusion of blood and colloid, anti-infection. Compared with clinical ARDS treatment

for over one week, this weakened the significance of the results. Finally, more molecular biological markers could be measured to help to discover the mechanism of treatment more clearly. All these should be under the considerations of future studies.

Conclusions

In summary, we established a severe ARDS model in aged Beagle dog with V-V ECMO to investigate the effects of different ventilation strategies on VILI and inflammatory response. We demonstrated that ultra-protective ventilation strategy can ameliorate the lung injury in aged dog model of severe ARDS supported with V-V ECMO than protective and conventional protective ventilation strategies. And the ultra-protective ventilation strategy significantly decreased the expression of inflammatory cytokines compared to protective and conventional protective ventilation strategies. This study can provide solid evidences for clinical treating on elderly patients with severe ARDS.

Abbreviations

V-V ECMO	Venovenous extracorporeal membrane oxygenation
ARDS	Acute respiratory distress syndrome
MV	Mechanical ventilation
CV	Conventional ventilation strategy
PV	Protective ventilation strategy
UPV	Ultra-protective ventilation strategy
VILI	Ventilator-induced lung injury
Pplat	Plateau pressure
VT	Tidal volume
RR	Respiratory rate
PEEP	Positiveend-expiratory pressure
EVLWI	Extravascular lung water index
COVID-19	Coronavirus disease 2019
PiCCO	Pulse indicator continuous cardiac output
HE	Hematoxylin and eosin
IOD	Integrated optical density

Declarations

Ethics approval and consent to participate

All experiment involving animals is provided Ethics approval and consent to participate by the Committee on Ethic of Medicine, Naval Military Medical University, PLA (No. 2021SL024).

Consent for publication

Not applicable.

Availability of data and materials

Parts of the data were submitted in supplementary documents. If anyone interested in this study and want to request the details and all of the data, please address directly to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zhinong wang and Jian Xiao designed the study and obtained research funding. Wang Xi, Anli Wang, Yufeng Zhang supervised the surgery, histological examination and data collection. Kai Liu, Jing Wang and Shiguan Le performed the V-V ECMO while Pengchao Cheng, Junnan Wang and Xiaofei Xue performed MV setting. Yue Yu and Pei Wang perfomed the all data analysis and paper modification. regarding the hematological disease and the transplant. All authors read and approved the final manuscript.

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Figures

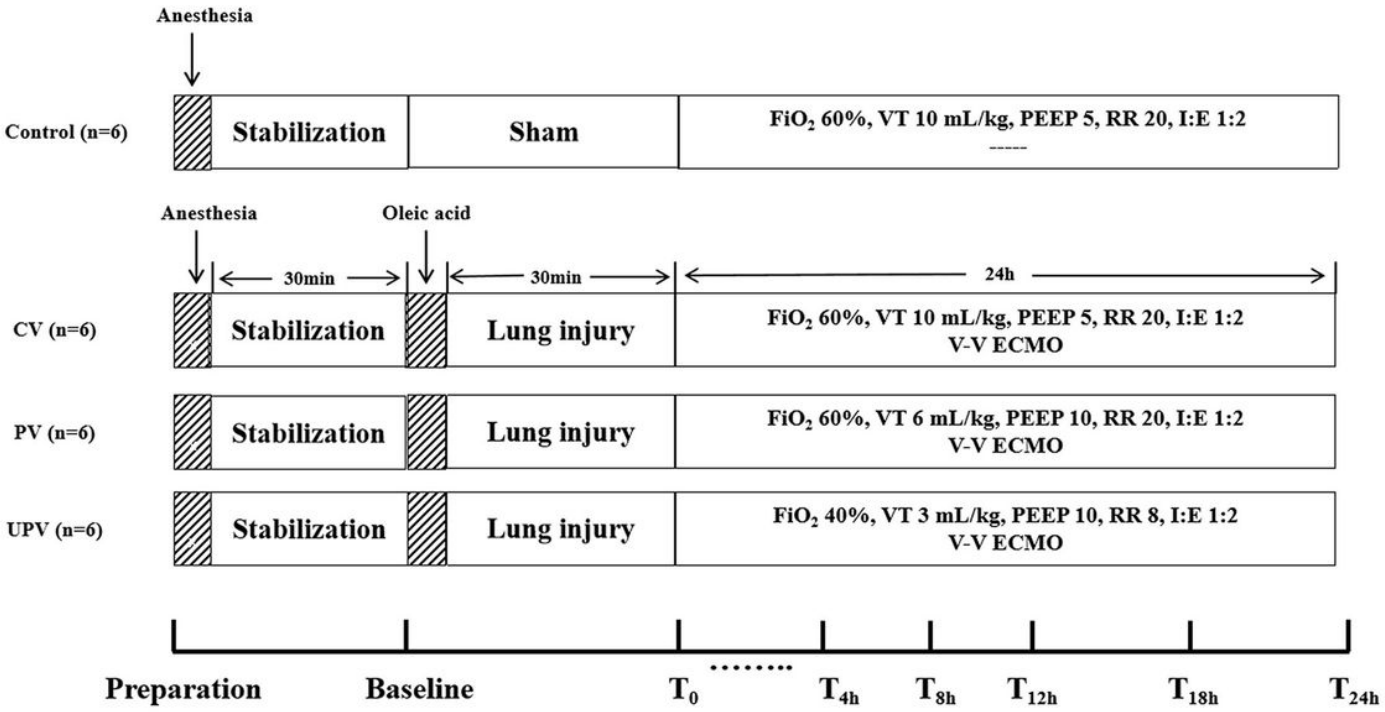

Figure 1

Study design and period. Data at T_0, T_{5min} T_{30min}, T_{1h}, T_{2h}, T_{4h}, T_{8h}, T_{12h}, T_{18h} and T_{24h} corresponds to the study period, during which each group received different ventilatory strategies.

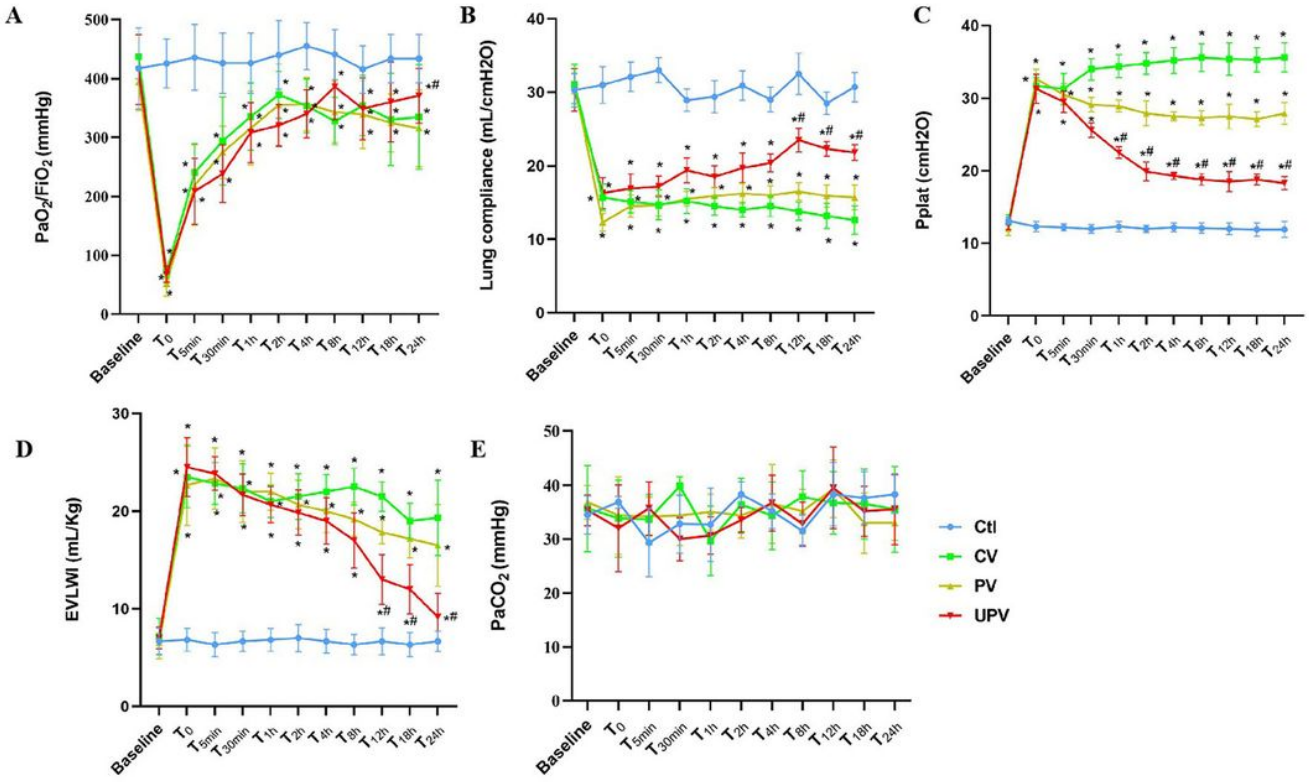

Figure 2

A: PaO_2/FiO_2 changes in the study period; B: Lung compliance changes during the study period; C: Pplat changes during the study period; D: EVLWI changes during the study period; E: $PaCO_2$ changes during the study period. Data at T_0, T_{5min} T_{30min}, T_{1h}, T_{2h}, T_{4h}, T_{8h}, T_{12h}, T_{18h} and T_{24h} corresponds to the study period, during which each group received different ventilatory strategies. * $p < 0.05$ compared to Control, $^{\#}$ $p < 0.05$ compared to PV group.

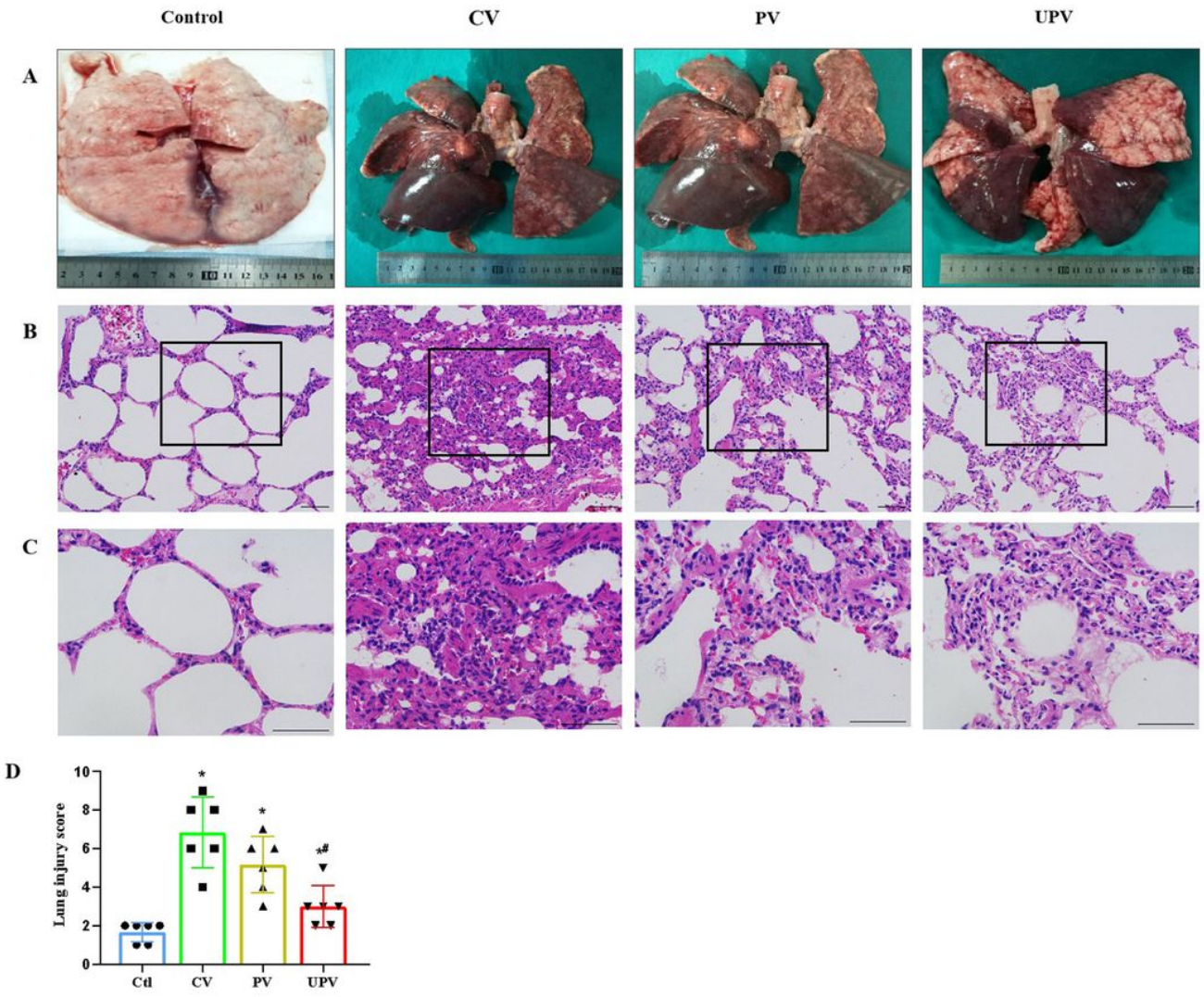

Figure 3

Gross specimen of lung in different groups; B: Representative photomicrographs appearances (magnification×200) of HE stain in different groups; C: Representative photomicrographs appearances (magnification×400) of HE stain in different groups; D: The lung injury scores in different groups. * $p <$ 0.05 compared to Control, $^{\#}p < 0.05$ compared to PV group. Scale bars: 50 μm.

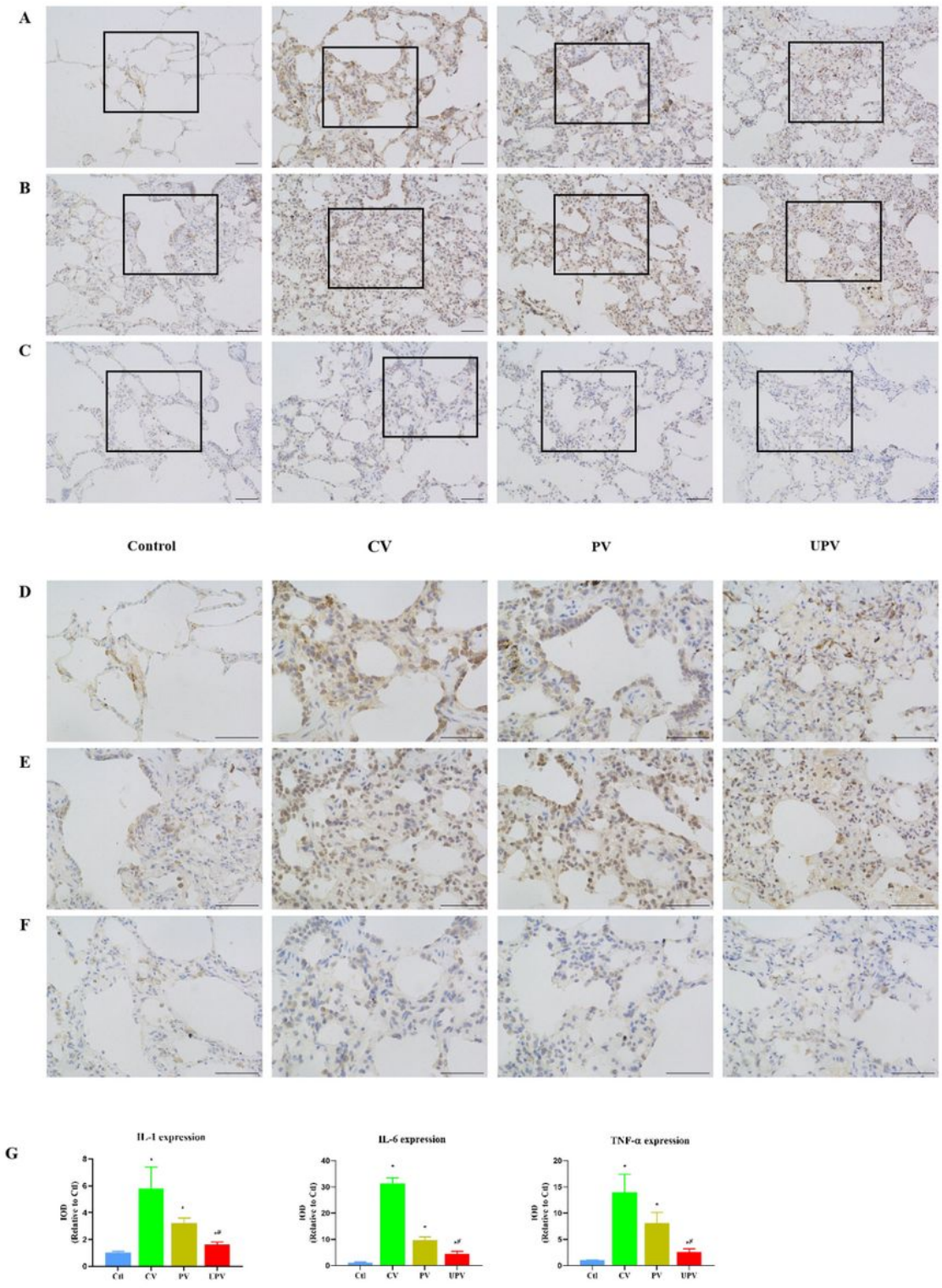

Figure 4

Representative immunohistochemistry photomicrographs appearances (magnification×200) of IL-6/ IL-10/TNF-α in lung tissue in different groups (A/B/C); Representative immunohistochemistry photomicrographs appearances (magnification×400) of IL-6/ IL-10/TNF-α in lung tissue in different groups (D/E/F); G: The expression of IL-6, IL-10 and TNF-α detected using Image Pro Plus in lung tissue of different groups.

Supplementary Files

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